I. At the bottom of page 2 of the Office Action, claims 71–91 were rejected under 35 U.S.C. §112, first paragraph.

Without capitulating to the position of the Examiner, in view of the new claims, it is believed that none of the issues the Examiner raised with respect to the now-canceled claims applies to the new claims. Accordingly, withdrawal of the rejection is in order.

II. At the bottom of page 3 of the Office Action, claims 71-93 were rejected under 35 U.S.C. §112, first paragraph.

The rejection is traversed for the following reasons.

The instant specification provides a detailed teaching of how to make and how to use recombinant AAV particles carrying a transgene expressing Factor IX.

As evidence that the instant specification provides an enabling disclosure, attached hereto are copies of publications that support the enablement of the teachings of the instant specification.

Snyder et al., 1997, Nature Genetics, 16:270-276, showed intraportal injection of 2.1, 4.2 or 8.4 x 10^{10} viral particles of rAAV-MFG-FIX and subsequent detection of expression by Western blot and ELISA (with a steady state concentration of 250-2000 ng/ml at week 36), see also Examples 5-10, Figure 8 and Figure 9 of the instant specification. The data indicate the expressed Factor IX was functional. Other data showed AAV transduction of liver and specifically hepatocytes. rAAV-MFG-FIX contains the Moloney murine leukemia virus (MLV) 5' LTR, adjacent splice donor acceptor sequences, the human FIX cDNA sequence and a bovine growth hormone polyA sequence, which is a vector used in the teachings of the instant specification.

Snyder et al, 1999, Nat Med 5:64-70, showed that intraportal infusion of rAAV results in the selective transduction of hepatocytes. Snyder et al. described expression of Factor IX and improved bleeding times following intraportal infusion of rAAV-MFG-FIX into hemophilia B mice. Constitutive expression of Factor IX was observed, which resulted in the correction of the bleeding disorder over a period of over 17 months. Mice with a steady-state concentration of 25% of the normal human level of Factor IX had normal coagulation. In dogs, a 1% level of expression of normal yielded an observable partial correction of a coagulation defect for at least 8 months.

Harding et al. (5th Annual Meeting of the American Society of Gene Therapy, 6/7/02, Boston, MA, abstract 478) described comparison of rAAV-MFG-FIX to an rAAV vector comprising the Factor IX transgene and a liver-specific promoter/enhancer ("LSP" consists of the rat thyroxine-binding globulin promoter (Tani et al., Endocrinology 1994 Dec;135(6):2731-6) and the human α1-microglobulin/bikunin enhancer (Rouet et al., J Biol Chem 1992 Oct; 267(29):20765-73), the combination of which is described in Ill et al., Blood Coagul Fibrinolysis 1997 Dec; Suppl 2:S23-30). Vectors were tested both in vitro and in vivo (via the intraportal and intravenous routes) and the results showed expression from both vector types with transduction primarily in the liver. Constructs which contained both the β globin intron and the woodchuck post-transcriptional regulatory element (WPRE) in combination with a liver-specific promoter yielded serum human Factor IX levels approximately 5X that achieved for rAAV-MFG-FIX. In each case, the levels remained stable for over 78 weeks.

In addition, a Phase I clinical study conducted by Dr. Bertil Glader, summary attached hereto, using an AAV particle expressing Factor IX has been initiated wherein an AAV vector encoding human FIX is administered into the hepatic artery.

The data provided in the specification and in the references show levels of expression that are sufficient for realizing a therapeutic effect.

With respect to the issue of making AAV, a number of different protocols that produce substantial yields of rAAV have been developed, for example, the use of helper viral vectors as compared to use of intact helper virus facilitate rAAV production. The instant specification and attached references demonstrate that sufficient AAV is obtained.

Methods for producing rAAV of sufficient titer for in vivo experiments were known in the art at the time the instant application was filed, see, e.g., U.S. Patent No. 5,354,678 (Lebkowski et al., issued 10/11/94, column 3, lines 41 – 51 and column 13, line 66 through column 14, line 58) and U.S. Patent No. 5,436,146 (Shenk et al., issued 7/25/95, column 5, line 55 through column 6, line 17 and column 12, lines 49 – 53 and column 13, lines 5 – 12).

On pages 3 through 8 of the Office Action, the Examiner made reference to a number of articles regarding the alleged unpredictability of AAV gene therapy and the purported inability of others to get sufficient virus production.

Contrary to the interpretation of Orkin et al., Russell et al., Fisher et al. and Chen et al. (pages 6-7 of the Office Action), at the time of filing the instant application, there were many examples of successful therapeutic gene transfer using AAV vectors.

For example, Kessler et al., PNAS, 93:14082-14087, 1996, described production of sufficient rAAV containing a gene for human erythropoietin (AAV-Epo) and the successful use of a single intramuscular administration into adult BALB/c mice that resulted in dose-dependent secretion of erythropoietin and a corresponding increase in red blood cell production (hematocrit) that persisted for up to 40 weeks.

In another example, delivery of 6×10^{10} AAV-tk-IRES-IL2 rAAV particles encoding both herpes simplex thymidine kinase and human interleukin-2 into a nude mouse model for glioma followed by administration of ganeyclovir resulted in a 35-fold reduction in the mean volume of tumors compared with controls (Okada et al., Gene Ther 1996 Nov; 3(11):957-64).

Furthermore, Applicants respectfully disagree with the Examiner regarding the disclosure in Koeberl et al. (PNAS, 94:1426-1431, 1997). That reference describes the enhanced effect of irradiation on in vivo expression of Factor IX in mice using a number of vectors (Fig. 1) including an AAV vector with the MLV LTR promoter, which the Examiner argued is nearly the same as that used in the instant application (page 7 of paper 22).

To the contrary, the Koeberl et al. vector differs from the rAAV-MFG vector described in the instant application by containing a second transgene (neo) under the control of an SV-40 promoter. Moreover, the Koeberl et al. vector does not include a splice donor acceptor site or intervening sequence

Koeberl et al. (PNAS, 94:1426-1431, 1997) stated that plasma levels of 100 ng/ml would prevent chronic disease (last paragraph, page 1430). As shown in Figs. 8 and 9 of the instant specification, Applicants were able to achieve plasma levels above 100 ng/ml. Thus the instant specification teaches expression of Factor IX sufficient to achieve a therapeutic effect.

Accordingly, a prima facie case of non-enablement has not been made. The instant application fully teaches how to make and how to use the claimed invention. Accordingly, the rejection can be withdrawn.

III. On page 11 of the Office Action, claims 71-85 were rejected under 35 U.S.C. 112, second paragraph.

Because those claims have been canceled, the rejection no longer applies. Moreover, it is believed that the issues raised by the Examiner do not apply to the new claims added hereinabove.

IV. At the bottom of page 12 of the Office Action, claims 71-91 were rejected under 35 U.S.C. §102(e) over Srivastava et al., U.S. Application Publication No. 2001/0051611.

The rejection is traversed for the following reasons.

Srivastava et al. provide a generic teaching on the use of rAAV. Srivastava et al. provide a generic listing of a large number of transgenes that are alleged to be usable in the practice of the method disclosed therein. However, there is no enabling disclosure of how to make or how to use such recombinant virus particles carrying any of essentially an unlimited number of transgenes. For example, there is no teaching that the Factor VIII gene is too large for packaging in an AAV particle.

Paragraph 25 of Srivastava et al. continues the generic listing of transgenes that are believed to be usable in the practice of the Srivastava et al. disclosure. But the working examples teach use of only galactosidase and globin.

Hence, inasmuch as the relied-on reference is not an issued patent but merely an application, there is no evidence or foundation that Srivastava et al. provide an enabling disclosure, particularly in light of the arguments above.

Moreover, without access to the priority document, benefit to the earlier priority date cannot be proved. Thus, if, arguendo, Srivastava et al. were considered enabling, it cannot be determined whether that disclosure is entitled to the priority dates. It is inequitable and improper to reject claims over a reference that is not fully available to the public.

Accordingly, the reference is ineffective against the claims of the instant invention and the rejection should be removed.

V. At the bottom of page 12 of the Office Action, claims 86-88 and 91 were rejected under 35 U.S.C. §102(e) over the Samulski et al. patent. Claims 86 and 89 also were rejected under 35 U.S.C. §103(a) over the same patent.

Samulski et al. do not teach each and every element of the claimed vectors. Hence, there is no anticipation and the rejection must be removed.

CONCLUSION

Applicants have taken substantial steps to advance prosecution. Reexamination, reconsideration, withdrawal of the rejections and early notification of allowance are solicited earnestly. If any questions remain unresolved, the Examiner is requested respectfully to contact the undersigned at the local exchange noted hereinbelow to facilitate prosecution. Finally, the Commissioner is authorized to charge Deposit Account No. 18-2220 for any fees that might arise in association with the instant Amendment.

Respectfully submitted,

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